## REMARKS

Claims 1, 2, and 4-10 are pending in this application. Claim 3 is canceled herein; claims 1, 2, and 4 are currently amended; and new claims 5-10 are added. Support for the amendments and new claims can be found throughout the specification and claims as filed, e.g., at page 2, lines 20-23, page 4, lines 7-14, page 5, lines7-9, and page 17, lines 8-10.

The amendments to the specification correct obvious errors in the dates and pages of cited publications. No new matter has been added.

35 USC § 102

Claims 1, 2, and 4 were rejected as being allegedly anticipated by Molina et al. (Food Research International, 32:135-143, 1999) and Flink (WO 99/37329). To anticipate a claim, the reference much teach every element of the claim. Neither Molina et al. nor Flink teaches or suggests an IgM immunoglobulin, as now recited in amended claim 1. Therefore, the claims are novel over Molina et al. and Flink.

35 USC § 103

Claim 3 was rejected as being allegedly unpatentable over Flink (WO 99/37329). Claim 3 has been canceled, and the claim element of an IgM has been incorporated into amended claim 1. The Office action, at page 7, acknowledges that Flink does not teach an IgM immunoglobulin. In fact, all of the functional examples of Flink's methods use a humanized IgG1 antibody. However, the Office action goes on to assert that, based on Flink's teachings that the preparations and methods described therein are suitable for the formulation of any antibody, one skilled in the art would predict a reasonable expectation of success that Flink's methods would be functional with IgM protein.

On the contrary, based on the art-recognized differences in the structure, stability, and precipitation properties of IgG and IgM antibodies, one skilled in the art would not have expected that the methods and formulations described by Flink would be functional for IgM.

Therefore, the Office action has not established a prima facie case of obviousness. These points are discussed in detail below.

The state of the art at the time of filing of the present application recognized that IgG and IgM immunoglobulins have differences in storage properties. Phillips et al. (Cytotherapy, 3:233-242, 2001, submitted herewith) teaches that purified IgM are prone to aggregate and precipitate on storage; that IgM aggregate and precipitate at pH < 3.5, conditions at which IgG are stable; and that storage of IgM at –20 °C led to substantial precipitation and loss of activity over 1-2 years (page 238). Phillips et al. goes on to conclude that "**extra work would be necessary . . . to find a suitable stabilizing formulation for the pure [IgM] Ab**" (page 238). The instant specification also teaches that production of a highly concentrated and stable IgM solution is difficult, because of the low solubility of IgM and its instability as compared to IgG (page 2). Additionally, the specification further teaches that storage of IgM is especially difficult at low temperatures (e.g., 4 °C) used during formulation, purification, storage, and distribution of IgM therapeutics (page 2).

Further, Page and Thorpe (Methods Mol Biol., 80:113-119, 1999, submitted herewith) teaches that IgM and IgG have differences that require different purification procedures (page 114). For example, most IgM are insoluble at low ionic strength, and a weak salt solution will cause precipitation (ibid., page 115). Also, different conditions are required for pre-purification of IgG and IgM antibodies using polyethylene glycol (PEG). IgM precipitates at a 6% PEG concentration, wherein IgG requires a 20% PEG concentration for precipitation (ibid., page 116). It is clear that the art recognized substantial differences in storage, stability, and precipitation properties between IgG and IgM antibodies that would not lead one skilled in the art to predict that conditions suitable for storage of IgG antibodies would also be suitable for IgM antibodies. Therefore, applicants submit that a prima facie case of obviousness over Flink has not been made.

Further, Flink does not teach or suggest the claim element of an IgM at a concentration of 20 mg/ml. Flink provides "an isotonic pharmaceutical formulation comprising an antibody and a buffer, wherein the antibody is present at 0.5mg/ml to 10mg/ml," and the only functional

examples provided by Flink utilize IgG1 at a concentration of 1 mg/ml. Based on the art-recognized differences in storage, stability, and precipitation properties between IgG and IgM antibodies, one skilled in the art would not predict that citric acid buffer would stabilize IgM at a concentration of 20 mg/ml—twice the maximal antibody concentration taught by Flink and twenty times the concentration used in the working examples.

Even if a prima facie case of obviousness has been made, secondary considerations here lead to a conclusion of nonobviousness. The results described in the instant specification that IgM can be successfully stored in citric acid buffer at 4 °C are unexpected in view of the art-recognized differences between IgG and IgM antibodies. In Example 1, applicants demonstrate successful storage of IgM solutions in citric acid buffer at 4 °C at IgM concentrations of up to 50 mg/ml, whereas precipitation was clearly observed at these IgM concentrations in acetic acid buffer (see FIG. 1). These unexpected results clearly provide evidence that the currently pending claims are nonobvious.

Further, the present application provides an unsolved need where others have failed. As noted above, the instant specification teaches that production and storage of a highly concentrated and stable IgM solution is difficult, especially at low temperatures used during formulation, purification, storage, and distribution of IgM therapeutics (page 2). Phillips et al. echoes this conclusion in its statement that additional work was required "**to find a suitable stabilizing formulation for the pure [IgM] Ab**" (page 238). It is notable that Phillips et al. was published in 2001, two years after the publication of the Flink reference. If the Office action were correct that Flink rendered use of citric acid buffer with IgM "obvious," Phillips et al. would not have still been looking for an answer to the IgM storage and stability problem two years after Flink published.

Applicants submit that the claims are not obvious over Flink, because no prima facie case of obviousness has been made and in view of additional evidence of nonobviousness. Applicants respectfully request reconsideration and withdrawal of the rejection for alleged obviousness.

## CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. This response is being submitted along with a Petition for Extension of Time and the required fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-158US1.

Respectfully submitted,

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